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ALTERATIONS IN SECRETORY PATTERNS FOLLOWING VAGOTOMY IN RATS WITH PAVLOV OR HEIDENHAIN POUCHES

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SUMMARY

1. In conscious rats provided with Pavlov or Heidenhain pouches, the acid and pepsin secretion in response to feeding and infusion of gastrin was established before and after truncal vagotomy. In Pavlov pouches the responses to 2-deoxy-D-glucose, methacholine and the combination of gastrin and methacholine were also studied.

2. Interdigestive secretion of acid and pepsin after vagotomy was decreased in the Pavlov pouch and increased in the Heidenhain pouch.

3. The acid response to feeding in the Pavlov pouch was substantially reduced after vagotomy, whereas the secretion of pepsin was only slightly diminished.

4. In the Heidenhain pouch after vagotomy, feeding augmented the high interdigestive secretion.

5. After vagotomy, the acid dose–response curve to gastrin was shifted to the right in the Pavlov pouch and to the left in the Heidenhain pouch.

6. In the Pavlov pouch after vagotomy, the acid response to the highest dose of methacholine employed was significantly enhanced.

7. A background infusion of methacholine reestablished in the Pavlov pouch the reduced responsiveness to gastrin following vagotomy.

8. Pepsin secretion was stimulated by gastrin in the Heidenhain pouch and after vagotomy in the Pavlov pouch. The stimulatory effect of methacholine on pepsin secretion in the Pavlov pouch was increased after vagotomy.

INTRODUCTION

This laboratory has introduced the conscious rat as an alternative to the conscious dog in investigations of various aspects of gastric secretion (see Kahlson, Rosengren & Svensson, 1973, for references). The main object of our earlier studies has been to describe the secretory response

to food and to assess the effects of the individual components operating on feeding. This has been done in conscious rats provided with classical Pavlov and Heidenhain pouches. Further, a standardized technique has been evolved that permits quantitative collection of gastric juice by perfusing the pouches. Administration of secretory agents has been done intravenously in graded doses.

We have recently shown that in the rat the Pavlov pouch was more sensitive to histamine and gastrin than the Heidenhain pouch (Svensson, 1970; Johansson, Lundell, Rosengren & Svensson, 1972). In these responses the rat resembles the dog. Furthermore, the responsiveness of the Heidenhain pouch to gastrin and histamine was enhanced by infusion of methacholine. Shay, Komarov & Gruenstein (1949) showed that truncal vagotomy in rats nearly completely abolished secretion in the pylorus ligated stomach. Similar observations have been reported in rats provided with a gastric fistula by Håkanson & Liedberg (1970, 1971), who also noted no secretory effects of a stable choline ester after vagotomy. It would thus appear that in the rat truncal vagotomy is followed by more profound effects on the responsiveness of the gastric mucosa than in other species and in the denervated Heidenhain pouch in the rat.

The purpose of the present study was to describe the effects of truncal vagotomy on interdigestive and gastrin-induced secretion in rats provided with Pavlov and Heidenhain pouches to elucidate the discrepancy between observations in stomach preparations after different methods of denervation.

METHODS

Animals. Female rats of the Sprague-Dawley strain, weighing 200–275 g, were used. They were fed a standard pellet diet (type 142, Teknosan, Malmö, Sweden), drank water freely and when provided with pouches had the choice of Tyrode solution.

Drugs. Hog gastrin II (donated by Professor Gregory, Liverpool), 2-deoxy-D-glucose (Sigma Chemical Co.) and methacholine chloride (Fluka AG) were used.

Stomach preparations. The operations were done under ether anaesthesia. Food was withheld for 15 hr before the operations. Pavlov pouches were created from the glandular part of the stomach, as described in detail elsewhere (Svensson, 1970). Heidenhain pouches were prepared in the main according to Alphin & Lin (1959). A period of at least 1 month was allowed for post-operative recovery.

Vagotomy. The abdominal cavity was approached through a mid line incision in the Heidenhain pouch rats and through a transverse incision proximally to the pouch in the Pavlov pouch rats. The anterior and posterior vagal trunks were cut and resected for at least 1 cm just below the diaphragm. To prevent gastric distension, a pyloroplasty was performed by making an incision 1 cm long through the anterior wall of the pyloroduodenal junction and closing the incision transversally. Post-operatively the rats were given 5·5% glucose and Tyrode solutions subcutaneously, for 3 days, whereafter the rats were allowed a liquid diet for another 3 days. Despite careful post-operative treatment, a mortality rate of about 50%

occurred in rats provided with Pavlov pouches. No mortality, however, was seen in rats provided with Heidenhain pouches. Secretory studies were resumed not earlier than 2 weeks after vagotomy.

Administration of secretory stimulants

Before an actual experiment, the non-vagotomized rats were fasted for 16 hr and the vagotomized animals for 24 hr, but they were allowed to drink water and Tyrode solution. During the period of observation, the rat was kept in a restraining cage of the Bollman type. Rats, in which the response to a meal was studied, had been trained to eat in the Bollman cage, and food was available for 30 min. Before stimulation, interdigestive secretion was collected for 2 hr. When the stimulant was administered by I.V. infusion, a vein was freed in the tail or the neck and a polyethylene tube was inserted. The tube was connected to a motor-driven syringe, which delivered 0·9% NaCl at a rate of 2 ml./hr. On establishing dose–response curves, gastrin II or methacholine were infused in stepwise increasing doses, each dose for 90 min, whereafter the doses were successively doubled. When the dose–response curve for gastrin was superimposed on a background infusion of methacholine, this was started 1 hr before the lowest dose of gastrin. Vagal stimulation was effected by injecting 2-deoxy-D-glucose subcutaneously.

The responses to feeding and to graded doses of gastrin were established twice in each rate provided with a Heidenhain or a Pavlov pouch before and after vagotomy. The effect of 2-deoxy-D-glucose was established once before vagotomy and twice after vagotomy. With the Pavlov pouches, the observation period after vagotomy started and finished by investigating the response to 2-deoxy-D-glucose. The experiments with methacholine were performed once before and after vagotomy.

Collection of gastric juice

Gastric juice was collected in 30 min portions by a perfusing technique (Svensson, 1970). The perfusate was analysed for HCl by titration against 0·1 N-NaOH with phenol red as an indicator, and the pepsin output was determined by a slight modification of the method of Hunt (1948). Pepsin is expressed in μg, in terms of the activity of a commercial crystalline preparation of pepsin (lot 95B-1270, Sigma Chemical Co.) as proposed by Bitsch (1966).

RESULTS

Interdigestive secretion in Pavlov pouches

Interdigestive secretion was determined for 2 hr before any kind of stimulation was applied. In the feeding experiments, in which no I.V. catheters were inserted, the interdigestive acid secretion was $21{\cdot}2 \pm 1{\cdot}68$ (S.E. of mean) μequiv/30 min which fell to $9{\cdot}2 \pm 0{\cdot}64$ (S.E. of mean) μequiv/30 min ($P < 0{\cdot}001$) after vagotomy. Interdigestive pepsin secretion was reduced to a lesser degree, from $207 \pm 10{\cdot}1$ (S.E. of mean) μg/30 min to $176 \pm 10{\cdot}6$ (S.E. of mean) μg/30 min ($P < 0{\cdot}05$). The values given represent the mean of fourteen determinations, each based on four 30-min periods, in seven Pavlov pouches.

Secretory effects of 2-deoxy-D-glucose

2-deoxy-D-glucose, 200 mg/kg, was injected subcutaneously, once before and twice after vagotomy in seven rats provided with Pavlov pouches. Before vagotomy this compound consistently increased acid and pepsin secretion. The secretory response was similar to that noted in an earlier study (Svensson, 1970). After proper vagotomy, 2-deoxy-D-glucose evoked no detectable increase in acid and pepsin secretion. In two rats, 2-deoxy-D-glucose evoked a slight increase in acid and pepsin secretion. After re-vagotomy, no secretory response was obtained with this compound (Fig. 1*a*, *b*).

Response to food in the Pavlov pouch

The response to feeding was established twice before and after vagotomy in seven Pavlov pouches. Before vagotomy feeding produced a pattern of response previously shown to be typical for Pavlov pouches in rats. In the first 30-min period acid secretion rose from about 21 to about 80 μequiv/30 min. This high rate of acid secretion was maintained for another 3 hr, whereafter acid secretion declined. Pepsin secretion, by contrast, was increased for a shorter period of time. After vagotomy, feeding induced a significant increase in acid secretion from about 9 to about 25 μequiv/30 min. In each of eight 30 min periods investigated, the acid response to food was considerably less than before vagotomy, the reduction amounting to about 70%. Vagotomy slightly reduced food-induced pepsin secretion in comparison with the results obtained before vagotomy, although the reduction was not significant (Fig. 2*a*, *b*).

Secretory effects of gastrin in Pavlov pouches

Dose–response curves for gastrin in the range 0·01–1·28 μg/hr were established before and after vagotomy in seven Pavlov pouches. Before vagotomy, the threshold dose of gastrin, i.e. a dose that increased acid secretion significantly above the interdigestive secretion, was 0·02 μg/hr, and hence the responses were dose-dependent. On infusing gastrin in the dose of 1·28 μg/hr, acid secretion was 99·4 ± 8·81 (S.E. of mean) μequiv/30 min, and this is nearly the maximum obtainable with gastrin (Fig. 3*a*). Vagotomy strongly reduced the sensitivity to gastrin, shifting the dose response curve to the right. After vagotomy the threshold dose was about doubled (to 0·04 μg/hr) and on infusing gastrin in the dose of 1·28 μg/hr a maximum secretory response of merely 58·7 ± 5·91 (S.E. of mean) μequiv/ 30 min was obtained. Before vagotomy pepsin secretion was not significantly affected by gastrin, as shown earlier (Johansson *et al.* 1972).

After vagotomy, gastrin stimulated pepsin secretion but significantly so only for the dose 0·32 μg/hr ($P < 0{\cdot}05$) (Fig. 3*b*).

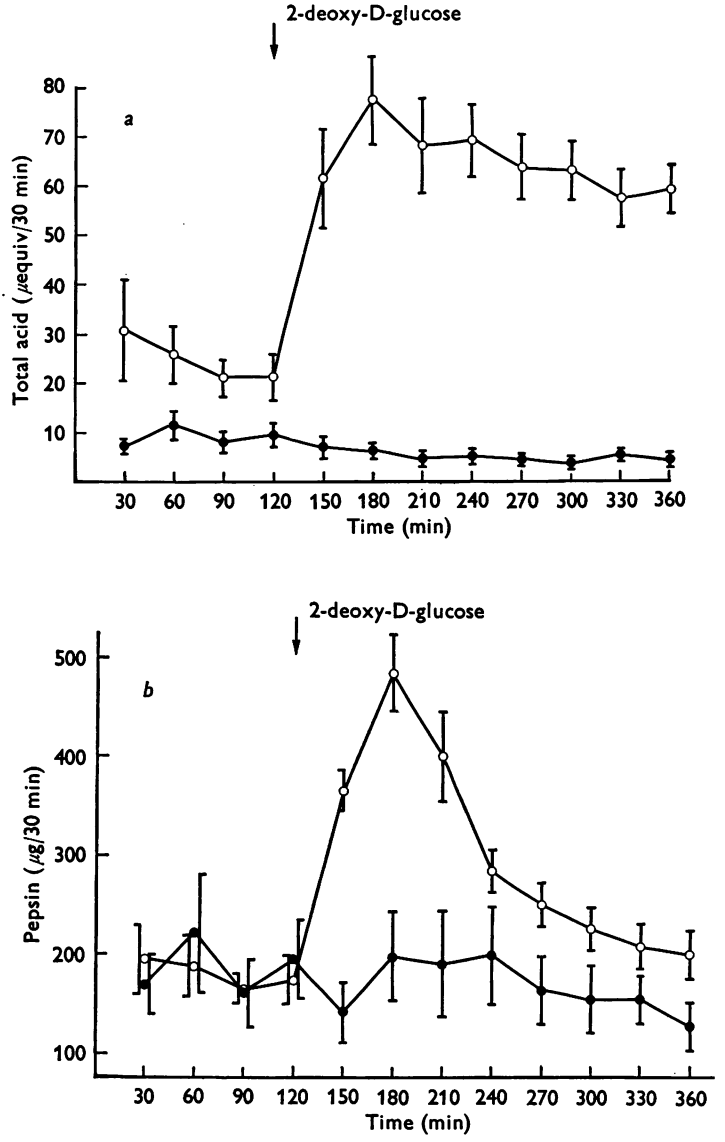

Fig. 1*a*, *b*. Acid (*a*) and pepsin (*b*) secretion in response to a s.c. injection of 2-deoxy-D-glucose, 200 mg/kg, in seven Pavlov pouches established once before (○—○) and twice after vagotomy (●—●). The vertical bars represent the S.E. of the mean.

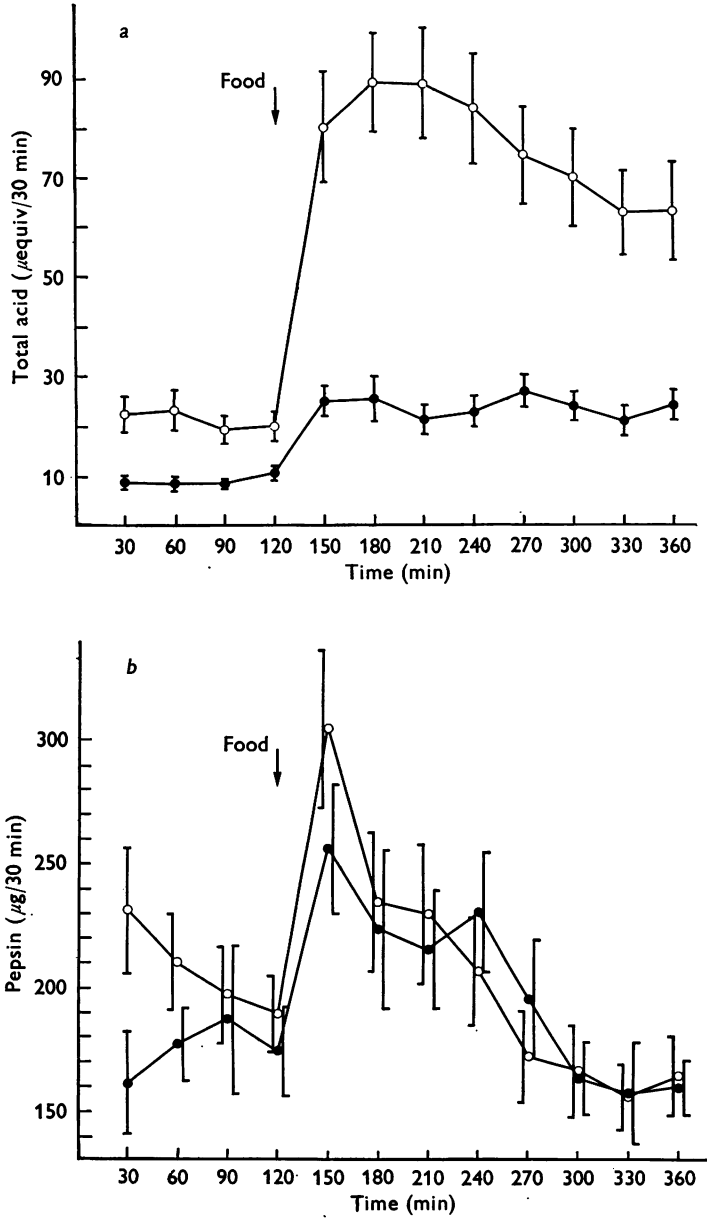

Fig. 2*a*, *b*. Acid (*a*) and pepsin (*b*) secretion in response to feeding in seven Pavlov pouches before (○—○) and after vagotomy (●—●). Each point is the mean of two determinations in each rat. The vertical bars represent the S.E. of the mean.

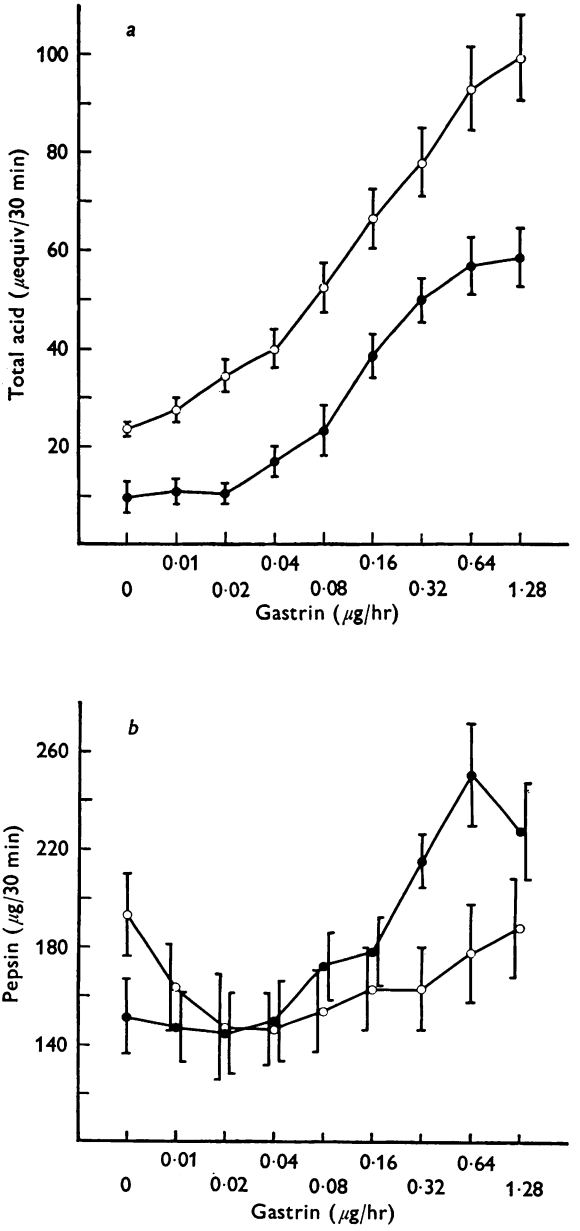

Fig. 3*a*, *b*. Acid (*a*) and pepsin (*b*) secretory responses in seven Pavlov pouches to I.V. infusion of gastrin II before (○—○) and after vagotomy (●—●). Each point represents the mean of determinations at the second and third 30 min period with two infusions in each rat. The vertical bars represent the S.E. of the mean.

Responses to methacholine in Pavlov pouches

Acid and pepsin secretory responses to methacholine in the dose-range 1–64 μg/hr were established in six Pavlov pouches. Before vagotomy, the acid secretory responses to methacholine were rather small compared with those obtained with gastrin and the dose–response curve was flat. After vagotomy, the dose–response curve was steepened in that the acid responses to small doses of methacholine were reduced and enhanced to larger doses, the difference between the two sets of responses being significant only for the dose 64 μg/hr ($P < 0{\cdot}01$). Pepsin secretion was stimulated by methacholine in the dose range 32–64 μg/hr. After vagotomy, the peptic cells became more sensitive to methacholine and gave strongly enhanced responses ($P < 0{\cdot}05$) to methacholine in the doses 8–32 μg/hr (Fig. 4*a* and *b*).

Responses to gastrin in combination with methacholine

In five rats with Pavlov pouches dose–response curves for gastrin were obtained after vagotomy, but now superimposed on a background infusion of methacholine in the dose of 10 μg/hr. The resulting dose–response curve was shifted to the left. The sensitivity to gastrin was not merely restored, but even exceeded the levels obtainable before vagotomy, a phenomenon especially pronounced with maximal infusions of gastrin (Fig. 5).

The background dose of methacholine was so chosen as to disclose the maximum secretory capability of the parietal cells. As to pepsin secretion, meaningful results were not obtainable on combining the stimulating agents, since the background dose of methacholine employed in itself stimulated pepsin secretion.

Interdigestive secretion in Heidenhain pouches

Interdigestive acid secretion in seven Heidenhain pouches before vagotomy was $1{\cdot}6 \pm 0{\cdot}15$ (S.E. of mean) μequiv/30 min which rose to $28{\cdot}5 \pm 4{\cdot}48$ (S.E. of mean) μequiv/30 min after vagotomy. In a group of Heidenhain pouches intended to be subjected to pyloroplasty alone, interdigestive acid secretion was $2{\cdot}7 \pm 0{\cdot}47$ (S.E. of mean) μequiv/30 min, a value which was not significantly altered by this type of surgery.

In the Heidenhain pouches following vagotomy, pepsin secretion increased from $128 \pm 14{\cdot}2$ (S.E. of mean) μg/30 min to $217 \pm 16{\cdot}2$ (S.E. of mean) μg/30 min, whereas no significant difference was noted in the control group after pyloroplasty alone.

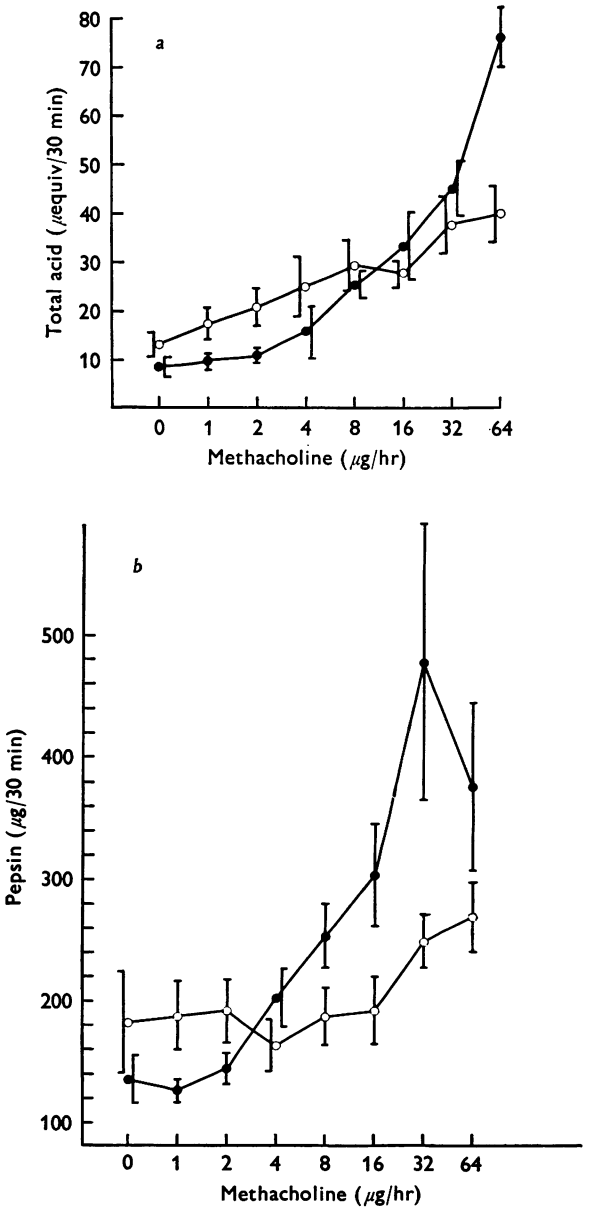

Fig. 4*a*, *b*. Acid (*a*) and pepsin (*b*) secretory responses in six Pavlov pouches to I.V. infusion of methacholine before (○—○) and after vagotomy (●—●). Each point represents the mean of determinations at the second and third 30 min period with one infusion in each rat. The vertical bars represent the S.E. of the mean.

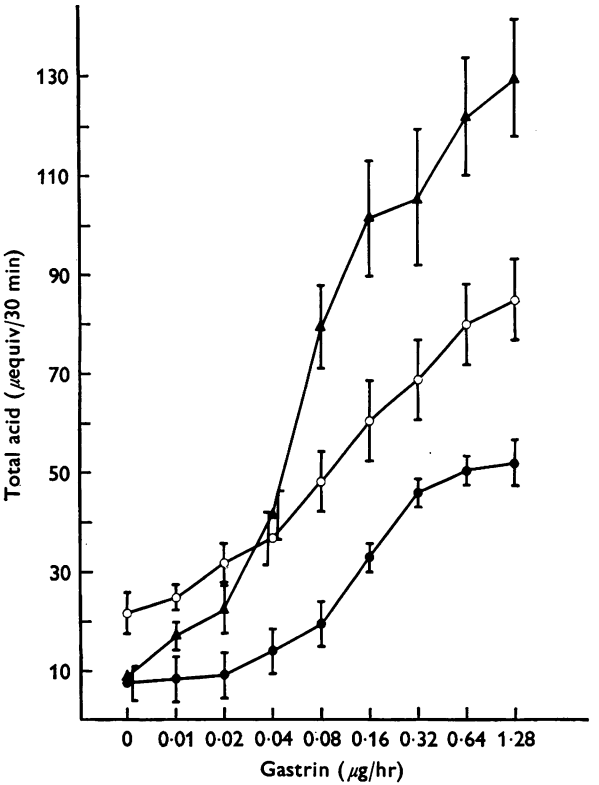

Fig. 5. Acid secretory responses in five Pavlov pouches to I.V. infusion of gastrin II before (○—○) and after vagotomy (●—●) and in combination with methacholine (10 μg/hr) after vagotomy (▲—▲).

Response to food in the Heidenhain pouch

Taking food for 30 min instituted in the Heidenhain pouch a typical pattern of response: the rate of acid secretion ascended steeply to a peak value in the first 30-min period, whereafter acid secretion was maintained for another 2 hr at a slightly lower level. The pepsin secretion in response to food was initially very high, due to the well known 'washing-out' effect, whereafter pepsin secretion proceeded for another hour. In the Heidenhain pouch, vagotomy raised the level of interdigestive secretion to the peak value obtained by food before vagotomy. However, on feeding still higher levels of acid secretion were noted, but only 60–90 min after onset of feeding. These results are summarized in Fig. 6*a*.

Pepsin secretion in response to food in the vagotomized group appeared slightly enhanced, save for the first 30 min period, presumably due to absence of the 'washing-out' phenomenon in pouches with a high inter-

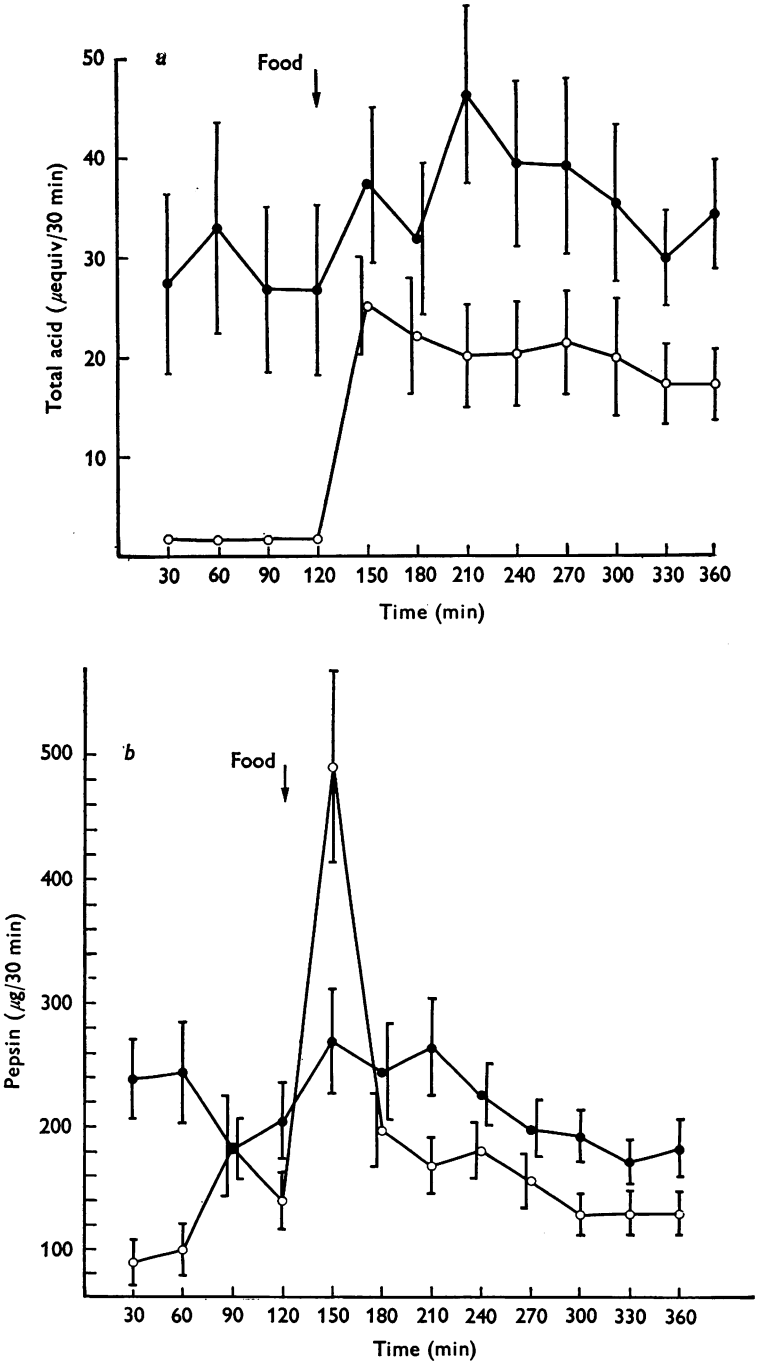

Fig. 6*a*, *b*. Acid (*a*) and pepsin (*b*) secretion in response to feeding in seven Heidenhain pouches before (○—○) and after vagotomy (●—●). Each point is the mean of two determinations in each rat. The vertical bars represent the S.E. of the mean.

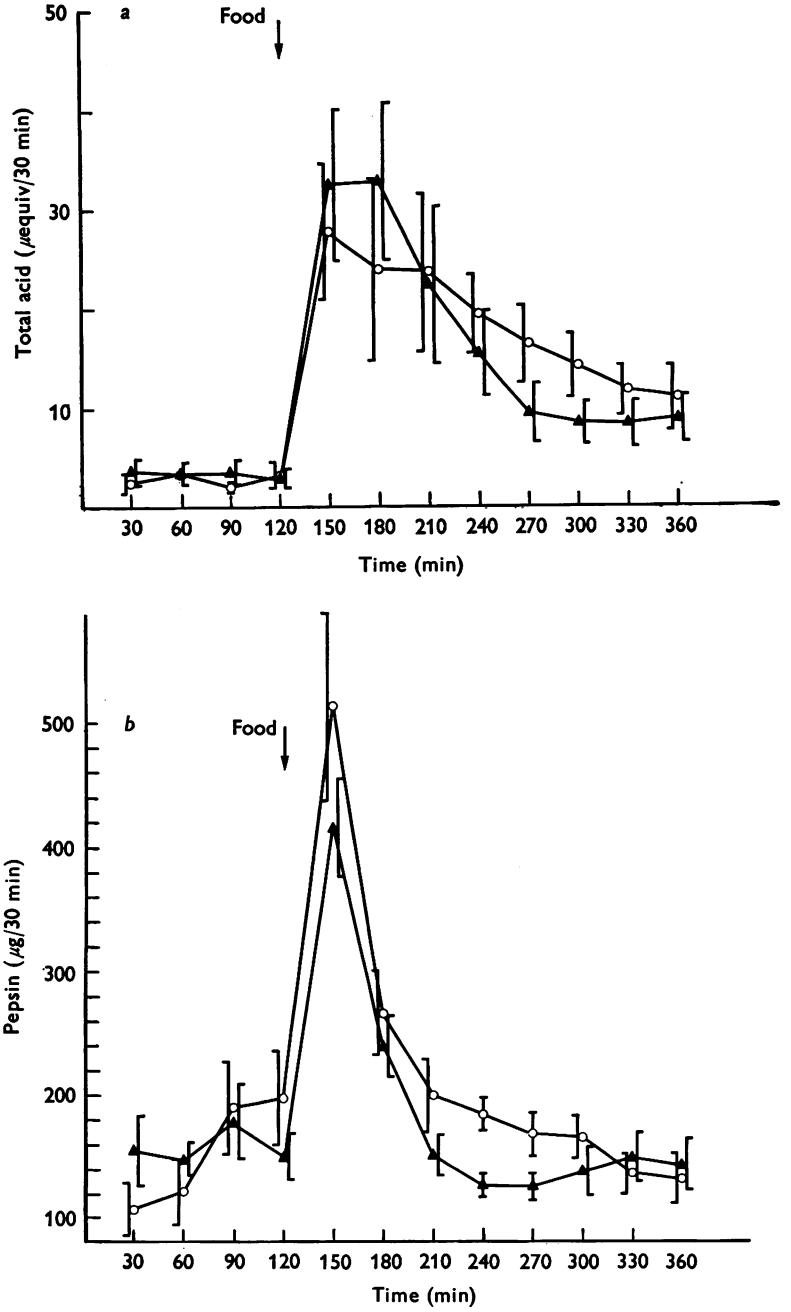

Fig. 7*a*, *b*. Acid (*a*) and pepsin (*b*) secretion in response to feeding in six Heidenhain pouches before (○—○) and after pyloroplasty (▲—▲). Each point is the mean of two determinations in each rat. The vertical bars represent the S.E. of the mean.

digestive secretion (Fig. 6*b*). Pyloroplasty alone did not change the pattern of acid and pepsin secretion in response to feeding as seen in Fig. 7*a* and *b*.

Secretory effects of gastrin in the Heidenhain pouch

Dose–response curves for gastrin, 0·02–2·56 μg/hr, were established in seven Heidenhain pouches. Vagotomy enhanced the acid secretory responses to infused gastrin in the whole dose range. The difference was significant for all doses of gastrin ($P < 0·05$), except for 0·16 μg/hr. This phenomenon was striking with the higher doses of gastrin.

Pepsin secretion was stimulated by infusion of gastrin in the Heidenhain pouch, as reported earlier (Svensson, 1970; Johansson *et al.* 1972). Vagotomy slightly enhanced the pepsin response to gastrin (Fig. 8*b*).

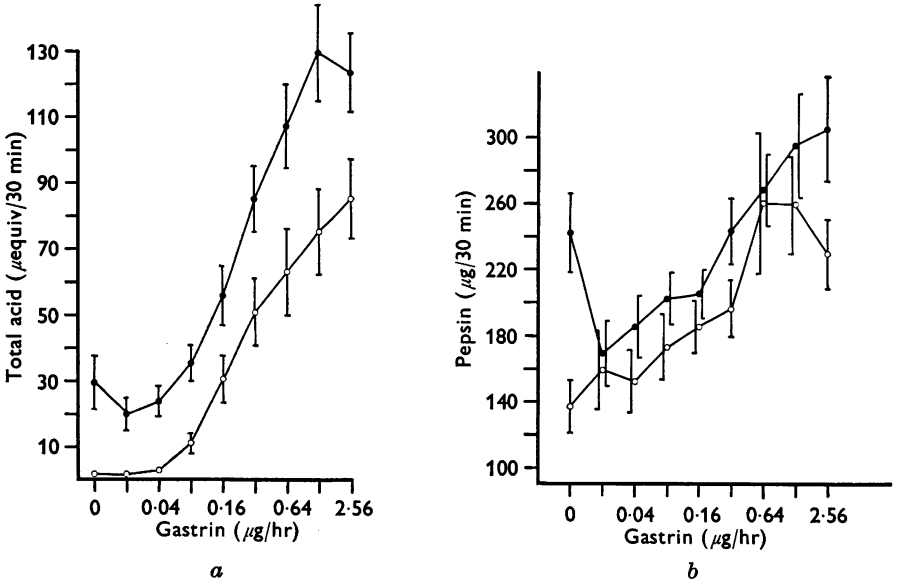

Fig. 8*a*, *b*. Acid (*a*) and pepsin (*b*) secretory responses in seven Heidenhain pouches to I.V. infusion of gastrin II before (○——○) and after vagotomy (●——●). Each point represents the mean of determinations at the second and third 30 min period with two infusions in each rat. The vertical bars represent the S.E. of the mean.

In the group of six Heidenhain pouch rats, subjected to pyloroplasty, a tendency towards increased acid responses to maximal infusions of gastrin was noted, although in the lower dose range no significant difference in the responses before and after pyloroplasty was noted. Pepsin secretion in response to gastrin was slightly enhanced in the dose range 0·32–2·56 μg/hr as seen in Table 1.

TABLE 1. Acid and pepsin secretion in six Heidenhain pouches in response to intravenous infusion of gastrin before and after pyloroplasty. Mean and S.E. of the mean are given. Nil stands for interdigestive secretion

	Nil	0·02	0·04	0·08	0·16	0·32	0·64	1·28	2·56
Acid before pyloroplasty	1·9 ± 0·51	2·4 ± 0·66	5·3 ± 1·23	12·2 ± 1·89 $P < 0·01$	34·9 ± 5·15 $P < 0·01$	49·7 ± 7·46 $P < 0·05$	70·0 ± 7·23	85·2 ± 10·12	102·9 ± 14·86
Acid after pyloroplasty	3·6 ± 1·05	2·8 ± 0·60	9·8 ± 2·78	23·7 ± 2·65	54·5 ± 5·86	97·4 ± 12·37	110·2 ± 12·17	128·1 ± 13·73	141·9 ± 16·49
Pepsin before pyloroplasty	148 ± 19·6	157 ± 15·5	191 ± 22·8 $P < 0·05$	209 ± 15·0	196 ± 9·5	219 ± 15·0	225 ± 12·1 $P < 0·05$	232 ± 17·5 $P < 0·05$	269 ± 23·0 $P < 0·05$
Pepsin after pyloroplasty	150 ± 16·3	150 ± 20·2	144 ± 7·8	214 ± 25·0	224 ± 20·2	340 ± 73·1	314 ± 37·5	318 ± 29·8	344 ± 16·2

DISCUSSION

The effect of vagal denervation on the secretory responses in different types of stomach preparations has been studied ever since Orbeli (1907) discovered that on converting a Pavlov pouch to a Heidenhain pouch the secretory response to a meal was substantially reduced. These experiments were largely extended by Hood & Code (1950). Unexpectedly, in dogs provided with a Heidenhain pouch, truncal vagotomy greatly increased the secretion of hydrochloric acid in 24 hr samples (Storer, Schmitz, Sauvage, Kanar, Diessner & Harkins, 1952) and in response to food (Lawson & Dragstedt II, 1968; Emås & Grossman, 1969). In attempts at explaining this phenomenon enhanced release of antral gastrin has been postulated (Evans, Zubiran, McCarthy, Ragins, Woodward & Dragstedt, 1953). However, the phenomenon persisted after partial (Dragstedt II, Johnson, Singer & Oberhelman, 1960) or total gastrectomy (Landor, 1964; Kelly, Nyhus & Harkins, 1964) in dogs subjected to truncal vagotomy, indicating involvement of factors other than increased antral gastrin. The problem has recently been approached employing techniques determining serum gastrin quantitatively. Yet, no consistent results have come forth in such determinations in the dog to establish the role of gastrin in the phenomenon under discussion (Korman, Brough & Hansky, 1972; Walsh, Csendes & Grossman, 1972).

In the present study, truncal vagotomy induced a substantial increase in interdigestive secretion in Heidenhain pouches as previously recorded in rats by Rees, Bjornsson & Thorbjarnarson (1968). The secretory responses to gastrin infusion in the whole dose range were also increased after vagotomy. Since the threshold dose was not altered after vagotomy, it would appear that the shift of the dose–response to the left was mainly due to the increase in the interdigestive secretion. The acid responses to the larger doses of gastrin cannot, however, be explained by increased interdigestive secretion. At present no approach can be envisaged permitting to disclose whether the increase in interdigestive secretion in the Heidenhain pouch is due to enhanced stimulatory or diminished inhibitory influence. In dogs, Emås & Grossman (1969) found submaximal and maximal responses to exogenous gastrin markedly increased in the Heidenhain pouch after vagotomy. These authors did not investigate the effect of pyloroplasty. In rats subjected to pyloroplasty alone, no alteration was noted in the rate of interdigestive secretion and in the responses to small infusions of gastrin. With larger doses of gastrin, there was a tendency to enhanced responses but the difference was significant only for some dosages. Pyloroplasty, perhaps, brings about alterations in the pH of the

antrum or in the gastrointestinal motility, in some respects similar to changes occurring on vagotomy.

Feeding induces in a rat Heidenhain pouch a rapid onset of secretion indicating effective recruitment of humoral stimuli during the cephalic phase as has also been noted in denervated pouches in dogs (Gregory & Tracy, 1960) prepared as devised by Gregory (1958). After vagotomy in the rat, the peak of the feeding response was delayed and the percentage increase above the interdigestive secretion was lowered.

The dog differs from man in the effect of truncal vagotomy on acid secretion induced by maximal stimulation by histamine or gastrin. In man truncal vagotomy reduces the acid secretion evoked by histamine by about 50–60% (Gillespie, Clark, Kay & Tankel, 1960; Payne & Kay, 1962; Broomé, Bergström & Olbe, 1967), whereas in vagotomy in dogs provided with a gastric fistula the maximal secretory response to histamine is not apparently altered (Emås & Grossman, 1967*a*, 1969). These authors further found that in dogs the maximal secretory response to gastrin and histamine was equal and remained unchanged after vagotomy. After vagal denervation in man, in contrast to the dog, the maximal secretory response to pentagastrin is reduced by about 60% (Payne, Cox, Spencer & Cheng, 1967; Aubrey & Forrest, 1970) i.e. similar to the situation in the rat.

In cats provided with a gastric fistula, vagotomy reduces the maximal responses to histamine and gastrin by about 30% (Emås & Grossman, 1967*b*).

In rats with a Pavlov pouch, completely vagotomized, as judged by the absence of secretory responses to 2-deoxy-D-glucose, interdigestive secretion and the response to a meal were strikingly reduced. Truncal vagotomy also reduced the sensitivity to exogenous gastrin and diminished the maximal secretory response by about 40%. Our results are at variance with those of Håkanson & Liedberg (1970, 1971), who reported that in the gastric fistula rat vagotomy completely abolished the response to pentagastrin. This discrepancy is possibly explained by contamination of gastric juice with saliva, escape of some of the secretion via the pyloroplasty, and/or regurgitation of duodenal contents and consequent neutralization of gastric juice in the gastric fistula preparation employed by these authors.

In the rat, the Heidenhain pouch is less sensitive to gastrin and histamine than is the Pavlov pouch (Svensson, 1970; Johansson *et al.* 1972). In the Heidenhain pouch, methacholine evokes a maximal acid secretory response about twice that obtainable with gastrin (Svensson, 1970). In the Pavlov pouch, by contrast, methacholine is a weaker stimulant of acid secretion than gastrin. After vagotomy, however, the maximal acid response to methacholine infusion was higher than that obtained with

maximal infusion of gastrin. It would thus appear that the secretory behaviour of the Pavlov pouch after vagotomy resembles that of the Heidenhain pouch. There are further characteristics common to the two types of denervated stomach preparations, e.g. the increased pepsin secretion on gastrin infusion. The increase in pepsin secretion noted on feeding in the Pavlov pouch after vagotomy might be taken to reflect increased sensitivity of the peptic cells to gastrin.

There are numerous reports on morphological changes in the gastric mucosa after vagotomy. Convincing evidence of an atrophy of the parietal cells following vagotomy has not been provided in man (Melrose, Russell & Dick, 1964) or in the rat (Sander, 1965; Crean, Gunn & Rumsey, 1969). Our observation that a background infusion of methacholine not merely restores but even increases the maximal secretory response to gastrin obtained before vagotomy indicates that vagotomy deprives the parietal cells of facilitating influences.

The observations on the rate of interdigestive acid secretion and the response to feeding in the Pavlov pouch deserve a few comments. The interdigestive secretion in the rat is predominantly sustained by the combined influence of antral gastrin and the vagus nerve. In the Heidenhain pouch, interdigestive acid secretion is in the range of 1–2 μequiv/30 min, whereas in the innervated Pavlov pouch the rate is at least 10 times larger although the pouches are of about the same size. Truncal vagotomy in rats induces opposite effects on interdigestive secretion, decrease in the Pavlov pouch and increase in the Heidenhain pouch. It would thus appear that the absence of vagal influence on the Pavlov pouch is more decisive for the secretory rate than the changes in humoral factors, which increase the interdigestive secretion in the Heidenhain pouch.

Finally, it should be emphasized that the rat resembles man closer than does the dog in the effect of truncal vagotomy on the responsiveness of the parietal cell.

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